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INTRODUCTION

Diabetes Mellitus is a chronic disease whose complications of blindness, amputations, kidney failure, and cardiovascular disease are devastating in both their human and financial costs. Although it has been clearly demonstrated that complications can be prevented by improving blood glucose (BG) levels, achieving the levels of glycemic control necessary has proved to be an elusive target. The development of portable glucose meters has empowered patients to perform home blood glucose monitoring (HBGM), however, getting patients to do so has been difficult because each test requires a sometimes painful finger-stick (FS) to obtain blood for the test and the cost per test (about 50 cents) is limiting. Thus, the technology to monitor BG non-invasively and inexpensively has been the "Holy Grail" of diabetes management. Numerous investigators have used a variety of technologies in an attempt to produce a non-invasive monitor. Because of both technical and performance limitations, however, only one device (GlucoWatch G2) has been approved and this has been shown to be inaccurate at clinically important low glucose levels.

It is highly desirable to have a simple and cost-effective way for patients to self-monitor blood glucose levels without using invasive devices such as lancets in combination with commercially available glucose meters. A non-invasive glucometer would provide subjects and health care providers with the same information obtained with standard devices, but without the pain, blood loss and potential for infection associated with invasive glucose meters. The ability to self-monitor blood glucose readings without the need for invasive devices could not only reduce the morbidity associated with commercially available glucometers, but it could potentially provide a significant cost-saving to the military medical system.

The ability to non-invasively monitor one's metabolic status without the need for an invasive device has particular relevance to the military community, both the warfighter and patients. While we planned only to use this device to measure glucose, the Nostix device also has the capability of measuring tissue hydration, oxygen, hematocrit, albumin and other important parameters of health. Thus, when enabled with wireless technology and an alarm, this device would permit the warfighter's hydration and metabolic status to be monitored both on site and at a distance thus alerting the soldier and his/her commander of critical health status changes. For beneficiaries of military health care who have diabetes, a non-invasive method of measuring glucose levels allows patients to check glucose levels at any time without stopping to prepare and use the equipment (glucometer, strips, lancets, & lancing device) required to obtain a FS specimen. The portability of the monitor and the ease with which BG levels can be obtained lends itself to more frequent monitoring as well as rapid recognition and treatment of high and low BG levels. Faster recognition and treatment of hyperglycemia (high BG) and hypoglycemia (low BG) will decrease the development of short and long term complications, thus enhancing the well-being and performance of the individual and decreasing medical expenses. If ultimately equipped with an alarm, it would prevent dangerous nocturnal hypoglycemia and resultant seizures or loss of consciousness.

The primary objectives of our efforts are: 1) Determine the accuracy of non-invasive glucometer monitored blood glucose levels as compared to that of standard invasive glucometers; 2) Using the Clark Error Grid, determine whether or not errors in treatment would have occurred if the non-invasive device would have been used in place of the standard device.

BODY

This project involved the use of an experimental, non-invasive glucose monitoring device called Nostix. The Nostix device is a semiconductor laser-based near-infrared spectrophotometer (NIRS) developed to perform real-time photometric blood glucose measurements. It uses a probe, about 3 cm in length clipped on a finger. The device is low power and will expose subjects to low energy levels similar to that of a pulse oximeter. It is connected by cable to a computer and is designed to continuously and non-invasively monitor blood glucose concentrations. Our goal was to assess the accuracy and precision of this investigational device for detecting blood glucose concentration when compared to capillary finger-stick blood samples analyzed by a standard glucometer, the Hemocue® glucose meter, a laboratory-quality bedside glucose analyzer.

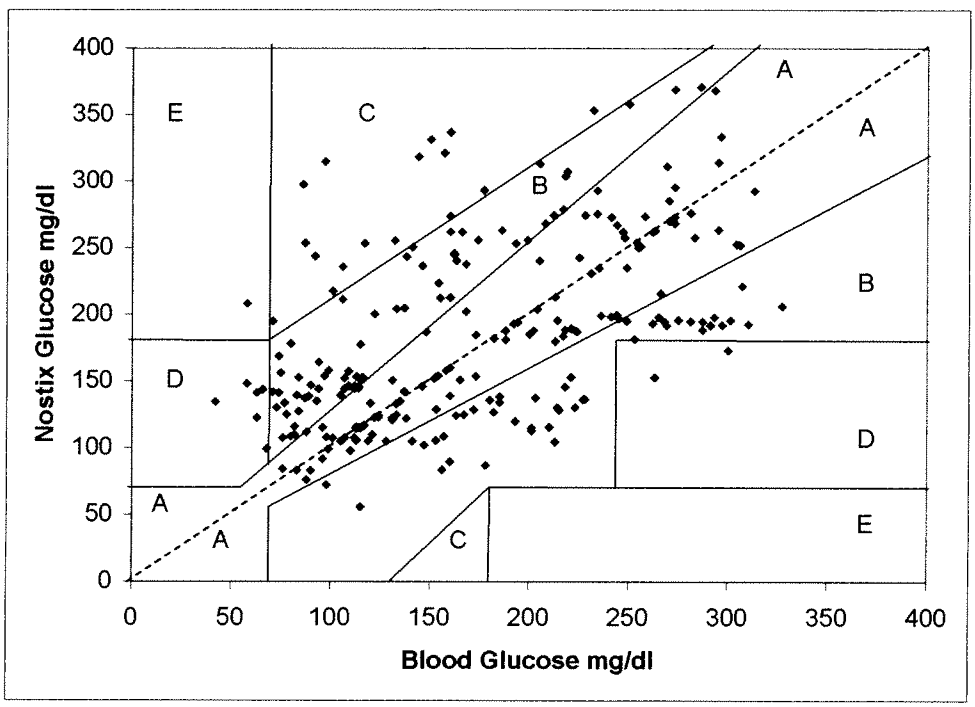
There were two primary objectives of this study: 1) determine if a non-invasive glucometer monitored blood glucose levels in patients with insulin-requiring diabetes mellitus with accuracy comparable to that of standard invasive glucometers. In order to achieve this objective, the investigators planned to compare the accuracy of this non-invasive device to a standard glucometer, the Hemocue® glucose meter, a laboratory-quality bedside glucose analyzer, in up to 45 subjects The second objective was to use the Clark Error Grid to determine whether or not errors in treatment (i.e. the wrong dose of insulin) would have occurred if treatment decisions were based on the non-invasive test results rather than fingerstick results using a standard glucometer.

KEY RESEARCH ACCOMPLISHMENTS

- A total of n=245 NIRS and HemoCue data pairs were collected from 15 subjects
- The computer software was upgraded several times in attempts to provide more accurate data analyses.
- Initially retrospective calibration indicated sufficient accuracy but when a prospective calibration was used it was not sufficiently accurate.
- The Clarke Error grid WR80106+b, shown below, contains n=245, r=0.563, MARD=37.1%. The key Clarke Error Grid statistic of the total of points in the A and B regions is n=219, or 89.4%. In order for a device to be approvable by the FDA, it should have at least 95% in the A+B regions.

Error Grid Statistics

A	B	A+B	C	D	E	Total Pairs
102	117	219	17	8	1	245
41.6%	47.8%	89.4%	6.9%	3.3%	0.4%	



n	r	MARD%	
245	0.563	0.371	WR80106 +b

- As detailed above, findings demonstrated that the correlation between the Nostix non-invasive measurements and fingerstick blood glucose measurements was inadequate for clinical use when a prospective rather than retrospective algorithm was applied.
- Subject accrual has been suspended pending technical modifications of the device.
- Additional efforts are underway to refine the device and the analytical algorithms to more accurately monitor glucose levels non-invasively.

REPORTABLE OUTCOMES

- CPT Abel Alfonso MC presented an abstract of the device and study at the Annual Meeting of the Endocrine Society in San Francisco in June 2006
- There have been no other manuscripts or abstracts, patents or licenses applied for or issued, or degrees obtained that are supported by this award.
- There has been no development of cell lines, tissues or serum repositories or informatics.
- No additional funding has been requested for the development or use of this device.
- Funding for this study supported a full-time project officer for the period of time identified in this report and purchase of equipment necessary to the study.
- Nostix LLP has continued to attempt to refine their technology in order to provide a non-invasive method of accurately measuring glucose levels as well as other indicators of one's metabolic status.

CONCLUSIONS

The initial results did not demonstrate the expected accuracy of the Nostix device, consequently the device is currently being redesigned by the manufacturer. Possible explanations of why the device failed to meet its goals include:

- Motion artifact of the probe which extended beyond the fingertip and thus, did not secure the emitter and detector from lateral motion.
    1. This may have caused a different tissue sample volume for each NIRS reading.
    2. Since the glucose absorbance is very small compared to that of water and hemoglobin different sample volumes may have slightly different water and hemoglobin levels that obscured the glucose absorbance.
- Systole of the cardiac cycle is used as a trigger to begin sampling because the optical absorbance by glucose is most consistent over time during systole.
    1. Some subjects had a weak pulse because of compromised circulation caused by diabetes.
    2. Some subjects began with an acceptable pulse amplitude, but experienced a decline in this level over the course of the study due to peripheral cooling or inactivity. (To minimize the affect of motion artifact, we asked the subjects to not move their hand).

Based on the findings of 15 subjects who were enrolled in the study, the device manufacturers are attempting to develop a reliable method of non-invasive glucose monitoring that would include the following refinements:

1. Eliminate motion artifact. Nostix is currently developing more stable probe designs which will reduce motion-related interference. Alternative sampling sites are also being assessed.
2. Improve signal output. Nostix has experimented with different methods to accomplish this and all possible solutions require more proprietary NIR emitters. Nostix is pursuing a vendor for such devices and has received estimated delivery times of 6-9 months since such an order would entail the production of custom semiconductor devices.
3. Improve the analytical algorithm. Use a multi-point calibration collected over 8 hours to then determine which of 132 possible weightings is most accurate in a particular patient and then apply that algorithm to future measurements.

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APPENDICES

N/A

SUPPORTING DATA

N/A